PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 295/08, A61K 31/40 — A1

(11) International Publication Number: WO 97/16434

(43) International Publication Date: 9 May 1997 (09.05.97)

(21) International Application Number: PCT/IB96/01049

(22) International Filing Date: 4 October 1996 (04.10.96)

(30) Priority Data:
60/006,125 2 November 1995 (02.11.95) US

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CHIU, Charles, K. [GB/US]; 12 Devon Drive, Pawcatuck, CT 06379 (US). MELTZ, Morgan [GB/US]; 115 Roxbury Road, Niantic, CT 06357 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: (-) CIS-6(S)-PHENYL-5(R)[4-(2-PYRROLIDIN-1-YLETHOXY)PHENYL]-5,6,7,8-TETRAHYDRONAPHTHALEN-2-OL D-TARTRATE

(57) Abstract

An advantageous process for the preparation of (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

(-) CIS-6(S)-PHENYL-5(R)[4-(2-PYRROLIDIN-1-YL ETHOXY) PHENYL]-5,6,7,8-TETRAHYDRONAPHTHALEN-2-OL D-TARTRATE

BACKGROUND OF THE INVENTION

The present invention relates to (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate which is useful as an estrogen agonist, and to a process for its preparation.

The preparation of (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, as its free base and R-binap salt is described in commonly owned United States patent application serial no. 08/369,954, the text of which is hereby incorporated by reference.

SUMMARY OF THE INVENTION

This invention is directed toward (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate.

In another aspect, this invention is directed toward a method of preparation of (-)cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate which comprises:

1) dissolving racemic or partially optically enriched cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in boiling aqueous ethanol to form a solution;

2) adding an equal molar amount of D-tartaric acid dissolved in aqueous ethanol to said solution to form a second solution;

3) cooling said second solution; and

4) collecting the product formed in step 3.

In another aspect, this invention provides a pharmaceutical composition comprising (-)cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate and a pharmaceutically acceptable carrier.

In yet another aspect, this invention provides methods for treating or preventing diseases or conditions which are susceptible to treatment or prevention by estrogen agonists which comprises administering to a mammal in need of such treatment or prevention an effective amount of (-)cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate.

optically active compounds. Resolution of this racemate has been previously accomplished by crystallization of the salt with R-(-)-1, 1` binaphthyl-2,2`-diyl hydrogen phosphate (R-binap) as described in commonly owned U.S. application serial no. 08/369,954. Since R-binap is not a suitable salt for pharmaceutical use, the R-binap product must be further converted to the free base and finally to a pharmaceutically acceptable salt.

D-tartaric acid has been found to form a 1:1 salt with racemic or partially optically enriched cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in aqueous ethanol.

Upon cooling, the desired (-) isomer separates as a solid and is easily collected, thus providing a pharmaceutically acceptable salt of the (-) cis isomer in high yield and purity in a single reaction step. Aqueous ethanol is the preferred solvent for this procedure; 95% aqueous ethanol is the preferred mixture.

This invention is readily carried out by dissolving racemic or partially optically enriched cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with an equal molar amount of D-tartaric acid in boiling aqueous ethanol; 95% ethanol is preferred. The amount of solvent must be adequate to effect complete solution of the salt. This has been found to be about 10 to 15mL per gram of racemic compound.

Upon cooling to room temperature, the desired (-) cis isomer separates as a solid. This product has an optical purity of about 95%. Washing with 95% ethanol under reflux produces a product with greater than 99% optical purity.

The compound of this invention is a valuable estrogen agonist and is useful for oral contraception; relief for the symptoms of menopause; prevention of threatened or habitual abortion; relief of dysmenorrhea; relief of dysfunctional uterine bleeding; relief of endometriosis; an aid in ovarian development; treatment of acne; diminution of excessive growth of body hair in women (hirsutism); the prevention and treatment of cardiovascular disease; prevention and treatment of atherosclerosis; prevention and treatment of osteoporosis; treatment of benign prostatic hyperplasia and prostatic carcinoma obesity; and suppression of post-partum lactation. This compound also has a beneficial effect on plasma lipid levels and as such are useful in treating and preventing hypercholesterolemia.

While the compound of this invention is an estrogen agonist in bone, it is an antiestrogen in breast tissue and as such would be useful in the treatment and prevention of breast cancer.

Control and Prevention of Endometriosis

The protocol for surgically inducing endometriosis is identical to that described by Jones, Acta Endoerinol (Copenh) 106:282-8. Adult Charles River Sprague-Dawley CD® female rats (200-240 g) are used. An oblique ventral incision is made through the skin and musculature of the body wall. A segment of the right uterine horn is excised, the myometrium is separated from the endometrium, and the segment is cut longitudinally. A 5x5 mm section of the endometrium, with the epithelial lining apposed to the body wall, is sutured at its four corners to the muscle using polyester braid (Ethiflex, 7-0®). The criterion of a viable graft is the accumulation of fluid similar to that which occurs in the uterus as a result of oestrogen stimulation.

Three weeks after transplantation of the endometrial tissue (+3 weeks) the animals are laparotomized, the volume of the explant (length x width x height) in mm was measured with calipers, and treatment is begun. The animals are injected sc for 3 weeks with 10 to 1000 mg/kg/day of the compound of this invention. Animals bearing endometrial explants are injected sc with 0.1 ml/day of corn oil for 3 weeks served as controls. At the end of 3 week treatment period (+6 weeks), the animals are laparotomized and the volume of the explant determined. Eight weeks after cessation of treatment (+14 weeks) the animals are sacrificed; the explant are measured again. Statistical analysis of the explant volume is by an analysis of variance.

Effect on Prostate Weight

Male Sprague-Dawley rats, three months of age are administered by subcutaneous injection of either vehicle (10% ethanol in water), estradiol (30 µg/kg), testosterone (1 mg/kg) or the compound of this invention daily for 14 days (n=6/group). After 14 days the animals are sacrificed, the prostate is removed and the wet prostate weight is determined. Mean weight is determined and statistical significance ($p<0.05$) is determined compared to the vehicle-treated group using Student's t-test.

The compound of this invention decreases prostate weight compared to vehicle. Testosterone has no effect while estrogen at 30 µg/kg reduces prostate weight.

Bone mineral density

Bone mineral density, a measure of bone mineral content, accounts for greater than 80% of a bone's strength. Loss of bone mineral density with age and/or disease reduces a bone's strength and renders it more prone to fracture. Bone mineral content is accurately measured in people and animals by dual x-ray absorptiometry (DEXA) such that changes as little as 1% can be quantified. We have utilized DEXA to evaluate changes in bone mineral density due to estrogen deficiency following ovariectomy (surgical removal of ovaries) and treatment with vehicle, estradiol (E2), keoxifen (raloxifen), or other estrogen agonists. The purpose of these studies is to evaluate the ability of the compounds of this invention to prevent estrogen deficiency bone loss as measured by DEXA.

Female (S-D) rats 4-6 months of age undergo bilateral ovariectomy or sham surgery and allowed to recover from anesthesia. Rats are treated by s.c. injection or oral gavage with various doses (10-1000 µg/kg/day, for example) of the compound this invention daily for 28 days. All compounds are weighed and dissolved in 10% ethanol in sterile saline. After 28 days the rats are killed and femora removed and defleshed. The femoral are positioned on a Hologic QDR1000W (Hologic, Inc. Waltham, MA) and bone mineral density is determined in the distal portion of the femur at a site from 1cm to 2cm from the distal end of the femur using the high resolution software supplied by Hologic. Bone mineral density is determined by dividing the bone mineral content by the bone area of the distal femur. Each group contains at least 6 animals. Mean bone mineral density is obtained for each animal and statistical differences ($p<0.05$) from the vehicle-treated ovariectomy and sham-operated group were determined by t test.

In vitro estrogen receptor binding assay

An *in vitro* estrogen receptor binding assay, which measures the ability of the compounds of the present invention to displace [3H]-estradiol from human estrogen receptor obtained by recombinant methods in yeast, is used to determine the estrogen receptor binding affinity of the compound of this invention. The materials used in this assay are: (1) Assay buffer, TD-0.3 (containing 10 nM Tris,

pH 7.6, 0.3 M potassium chloride and 5 mM DTT, pH 7.6); (2) The radioligand used is [3H]-estradiol obtained from New England Nuclear; (3) the cold ligand used is estradiol obtained from Sigma (4) recombinant human estrogen receptor, hER.

A solution of the compound is prepared in TD-0.3 with 4% DMSO and 16% ethanol. The tritiated estradiol is dissolved in TD-0.3 such that the final concentration in the assay was 5nM. The hER is also diluted with TD-0.3 such that 4-10 µg of total protein was in each assay well. Using microtitre plates, each incubate received 50 ul of cold estradiol (nonspecific binding) or the compound solution, 20 uL of the tritiated estradiol and 30 ul of hER solutions. Each plate contains in triplicate total binding and varying concentrations of the compound. The plates are incubated overnight at 4°C. The binding reaction is then terminated by the addition and mixing of 100 mL of 3% hydroxylapatite in 10 mM tris, pH 7.6 and incubation for 15 minutes at 4°C. The mixtures is centrifuged and the pellet washed four times with 1% Triton-X100 in 10 mM Tris, pH 7.6. The hydroxylapatite pellets are suspended in Ecoscint A and radioactivity is assessed using beta scintigraphy. The mean of all triplicate data points (counts per minute, cpm's) is determined. Specific binding is calculated by subtracting nonspecific cpm's (defined as counts that remain following separation of reaction mixture containing recombinant receptor, radioligand, and excess unlabeled ligand) from total bound cpm's (defined as counts that remain following the separation of reaction mixture containing only recombinant receptor, radioligand). Compound potency is determined by means of IC50 determinations (the concentration of a compound needed to inhibition 50% of the of the total specific tritiated estradiol bound). Specific binding in the presence of varying concentrations of compound is determined and calculated as percent specific binding of total specific radioligand bound. Data are plotted as percent inhibition by compound (linear scale) versus compound concentration (log scale).

Effect on total cholesterol levels

The effect of the compound of the present invention on plasma levels of total cholesterol is measured in the following way. Blood samples are collected via cardiac puncture from anesthetized female (S-D) rats 4-6 months of age that are bilaterally ovariectomized and treated with the compound (10-1000 µg/kg/day, for

example, sc or orally for 28 days or with vehicle for the same time), or sham operated. The blood is placed in a tube containing 30µL of 5% EDTA (10µL EDTA/1 mL of blood). After centrifugation at 2500 rpm for 10 minutes at 20°C the plasma is removed and stored at -20°C unit assay. The total cholesterol is assayed using a standard enzymatic determination kit from Sigma Diagnostics (Procedure No. 352).

Effect on obesity

Sprague-Dawley female rats at 10 months of age, weighing approximately 450 grams, are sham-operated (sham) or ovariectomized (OVX) and treated orally with vehicle, 17a ethynyl estradiol at 30 mg/kg/day or the compound of this invention at 10-1000 mg/kg/day for 8 weeks. There are 6 to 7 rats in each sub group. On the last day of the study, body composition of all rats is determined using dual energy x-ray abosorptiometry (Hologic QDR-1000/W) equipped with whole body scan software which shows the proportions of fat body mass and lean body mass.

A decrease in fat body mass indicates that the compound of this invention is useful in preventing and treating obesity.

The remedies for prostatic diseases, breast cancer, obesity, cardiovascular disease, hypercholesterolemia and osteoporosis containing the compound of this invention may be administered to animals including humans orally or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, injections, suspensions and syrups.

The remedies for prostatic diseases, breast cancer, obesity, cardiovascular disease, hypercholesterolemia and osteoporosis containing the compound of this invention can be prepared by the methods commonly employed using conventional, organic or inorganic additives, such as an excipient (e.g., sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (e.g., cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylprrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator (e.g., starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (e.g., magnesium stearate, light anhydrous silicic acid, talc or

sodium lauryl sulfate), a flavoring agent (e.g., citric acid, menthol, glycine or orange powder), a preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (e.g., citric acid, sodium citrate or acetic acid), a suspending agent (e.g., methylcellulose, polyvinylpyrrolidone or aluminum stearate), a dispersing agent (e.g., hydroxypropylmethylcellulose), a diluent (e.g., water), and base wax (e.g., cocoa butter, white petrolatum or polyethylene glycol). The amount of the active ingredient in the medical composition may be at a level that will exercise the desired therapeutical effect; for example, about 0.1 mg to 50 mg in unit dosage for both oral and parenteral administration.

The active ingredient may be usually administered once to four times a day with a unit dosage of 0.1 mg to 50 mg in human patients, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration. A preferred dose is 0.25 mg to 25 mg in human patients. One dose per day is preferred.

The term "treating" as used herein includes preventative (e.g. prophylactic) and palliative treatment.

PREPARATION I

Racemic cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl ethoxy) phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol

Step A

cis-1-{2-[4-(6-Methoxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine. A solution of 1-{2-[4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine hydrochloride (nafoxidene hydrochloride) (1.0 g, 2.16 mmol) in 20 mL of absolute ethanol containing 1.0 g of palladium hydroxide on carbon was hydrogenated at 50 psi at 20°C for 19 hours. Filtration and evaporation provided 863 mg (93%) of *cis*-1-{2-[4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine: ^{1}H-NMR ($CDCl_3$): d 3.50-3.80 (m, 3H), 3.85 (s, 3H), 4.20-4.40 (m, 3H), 6.80-7.00 (m, 3H); MS 428 (P^++1).

Step B

To a solution of 400 mg (0.94 mmol) of the product from Step A in 25 ml of methylene chloride at 0°C was added, dropwise with stirring, 4.7 ml (4.7 mmol) of

a 1.0 M solution of boron tribromide in methylene chloride. After 3 hours at room temperature, the reaction was poured into 100 ml of rapidly stirring saturated aqueous sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to afford 287 mg (74% yield) of the title substance as the free base. ^{1}H-NMR ($CDCl_3$): d 3.35 (dd, 1H), 4.00 (t, 2H), 4.21 (d, 1H), 6.35 (ABq, 4H). The corresponding hydrochloride salt was prepared by treating a solution of the base with excess 4N HCl in dioxane, followed by evaporation to dryness and ether trituration (MS: 415 [P^+ + 1])

An alternative method useful for Preparation 1 is described below.

Step A

1-{2-[4-(6-Methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine: A mixture of anhydrous $CeCl_3$ (138 g, 560 mmol) and THF (500 mL) was vigorously stirred for 2 h. In a separate flask, a solution of 1-[2-(4-bromophenoxy)ethyl]pyrrolidine (100 g, 370 mmol) in THF (1000 mL) was cooled to -78°C and *n*-BuLi (2.6 M in hexanes, 169 mL, 440 mmol) was slowly added over 20 min. After 15 min, the solution was added to the $CeCl_3$ slurry cooled at -78°C via cannula and the reaction was stirred for 2 h at -78°C. A solution of 6-methoxy-1-tetralone (65.2 g, 370 mmol) in THF (1000 mL) at -78°C was added to the arylcerium reagent via cannula. The reaction was allowed to warm slowly to room temperature and was stirred for a total of 16 h. The mixture was filtered through a pad of celite. The filtrate was concentrated *in vacuo* and 3 N HCl (500 mL) and Et_2O (500 mL) were added. After stirring for 15 min, the layers were separated. The aqueous layer was further washed with Et_2O (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to provide 6-methoxy-1-tetralone (22 g). The aqueous layer was basified to pH 12 with 5 N NaOH and 15% aqueous $(NH_4)_2CO_3$ (1000 mL) was added. The aqueous mixture was extracted with CH_2Cl_2 (2x). The organic solution was dried ($MgSO_4$), filtered, and concentrated to provide a brown oil. Impurities were distilled off (110-140°C @ 0.2 mmHg) to yield the product (74 g, 57%). ^{1}H NMR (250 MHz, $CDCl_3$): d 7.27 (d, J = 8.7 Hz, 2H), 6.92-6.99 (m, 3H), 6.78 (d, J = 2.6 Hz, 1H), 6.65 (dd, J = 8.6, 2.6 Hz, 1H), 5.92 (t, J = 4.7 Hz, 1H), 4.15 (t, J = 6.0 Hz, 2H), 3.80 (s, 3H), 2.94 (t, J = 6.0 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H), 2.66 (m, 2H), 2.37 (m, 2H), 1.84 (m, 4H).

Step B

1-{2-[4-(2-Bromo-6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine: Pyridinium bromide perbromide (21.22 g, 60.55 mmol) was added portionwise to a solution of 1-{2-[4-(6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine (23 g, 72 mmol) in THF (700 mL). The reaction was stirred for 60 h. The precipitate was filtered through a Celite pad with the aid of THF. The off-white solid was dissolved in CH_2Cl_2 and MeOH and was filtered away from the Celite. The organic solution was washed with 0.5 N aq HCl followed by satd $NaHCO_3$ (aq). The organic solution was dried ($MgSO_4$), filtered, and concentrated to provide a brown solid (21.5 g, 83%). ^1H NMR (250 MHz, $CDCl_3$): d 7.14 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 2.2 Hz, 1H), 6.55 (m, 2H), 4.17 (t, J = 6.0 Hz, 2H), 3.77 (s, 3H), 2.96 (m, 4H), 2.66 (m, 4 H), 1.85 (m, 4H).

Step C

1-{2-[4-(6-Methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine hydrochloride (Nafoxidene hydrochloride): To a mixture of 1-{2-[4-(2-bromo-6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine (19 g, 44 mmol), phenylboronic acid (7.0 g, 57 mmol), and tetrakis(triphenylphosphonium)palladium (1.75 g, 1.51 mmol) in THF (300 mL) was added Na_2CO_3 (13 g, 123 mmol) in H_2O (100 mL). The reaction was heated at reflux for 18 h. The layers were separated and the organic layer was washed with H_2O followed by brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield 17.96 g of a brown solid. The residue was dissolved in a 1:1 mixture of CH_2Cl_2 and EtOAc (250 mL) and 1 N HCl in Et_2O (100 mL) was added. After stirring for 2 h, product was allowed to crystallize from solution and 11 g of material was collected by filtration. Concentration of the mother liquor to half its volume provided an additional 7.3 g of product.

Step D

cis-1-{2-[4-(6-Methoxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine: 1-{2-[4-(6-Methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine hydrochloride (nafoxidene hydrochloride) (75 g, 162 mmol) was dissolved in 1000 mL of EtOH and 300 mL of MeOH. Dry $Pd(OH)_2$ on carbon was added and the mixture was hydrogenated on a Parr shaker at 50°C

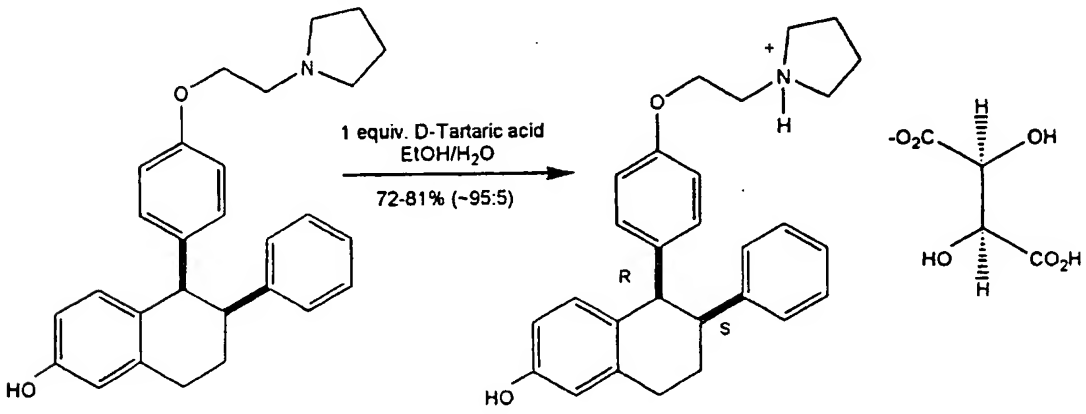
and 50 psi for 68 h. The catalyst was filtered off with the aid of celite and the solvents were removed *in vacuo*. The resulting white solid was dissolved in CH_2Cl_2 and the solution was washed with satd $NaHCO_3$ (aq). The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield an off-white solid (62.6 g, 90%).

Step E

cis-6-Phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol: A mixture of *cis*-1-{2-[4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine (12 g, 28 mmol), acetic acid (75 mL), and 48% HBr (75 mL) was heated at 100°C for 15 h. The solution was cooled and the resulting white precipitate was collected by filtration. The hydrobromide salt (9.6 g, 69%) was dissolved in $CHCl_3$/MeOH and was stirred with satd $NaHCO_3$ (aq). The layers were separated and the aqueous layer was further extracted with $CHCl_3$/MeOH. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield product as an off-white foam. ^1H NMR (250 MHz, $CDCl_3$): d 7.04 (m, 3H), 6.74 (m, 2H), 6.63 (d, J = 8.3 Hz, 2H), 6.50 (m, 3H), 6.28 (d, J = 8.6 Hz, 2H), 4.14 (d, J = 4.9 Hz, 1H), 3.94 (t, J = 5.3 Hz, 2H), 3.24 (dd, J = 12.5, 4.1 Hz, 1H), 2.95 (m, 4H), 2.78 (m, 4H), 2.14 (m, 1H), 1.88 (m, 4H), 1.68 (m, 1H).

EXAMPLE 1

(-) Cis-6(S)-Phenyl-5(R)-[4-(2-pyrrolidin-1-yl-ethoxy) phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-Tartrate



The racemic amine of Preparation 1 (5g, 12.1mmol) in a 95:5 mixture of absolute ethanol/water (50mL) was treated with a solution of D-tartaric acid (1.83g, 12.1mmol) in 95:5 mixture of absolute ethanol/water (20mL). The mixture was heated under gentle reflux and resulted in a homogeneous solution. After heating for 10 minutes, the mixture was allowed to cool and stir at ambient temperature (~25°C) overnight. The salt precipitated out as a white solids, and was collected by suction filtration, washed with absolute ethanol (20mL) and sucked dry. The collected white solids (3.75g) were dried further under house vacuum at room temperature (~25°C) to yield 2.77g (81% of theory). Chiral HPLC assay of the salt indicated an optical purity of 95:5 in favor of the desired enantiomer.

The white solids (2.77g) were suspended in a 95:5 mixture of absolute ethanol/water (28mL), heated under reflux with stirring for 3.5 hours. After cooling to room temperature, the mixture was granulated overnight. The white solids were collected by suction filtration, washed with ethanol (15mL) and sucked dry. After drying under house vacuum at room temperature, 2.48g (95% of theoretical yield) of the resolved salt was obtained with an optical purity of >99:1 as judged by chiral HPLC assay.

CLAIMS

1. A method of preparation for the compound (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-yl ethoxy) phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate which comprises:

a) dissolving racemic or partially optically enriched cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl ethoxy) phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in boiling aqueous ethanol to form a solution;

b) adding an equal molar amount of D-tartaric acid dissolved in aqueous ethanol to said solution to form a second solution;

c) cooling said second solution; and

d) collecting the product formed in step 3.

2. A method of treating osteoporosis in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.

3. A method of treating cardiovascular disease or hyperlipidemia in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.

4. A method of treating prostatic disease in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.

5. A method of lowering serum cholesterol levels in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of formula I.

6. A method of treating obesity in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.

7. A method of treating breast cancer in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.

8. A method of treating endometriosis in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.

INTERNATIONAL SEARCH REPORT

Interna: Application No
PCT/IB 96/01049

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/08 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 12, no. 5, September 1969, page 881-885 XP002019481 DANIEL LEDNICER ET AL: see page 883 ---	1
P,A	WO,A,96 21656 (PFIZER,INC.) 18 July 1996 cited in the application see page 12, line 1-5; claims -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 1996	10. 01. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Luyten, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 96/01049

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 2-8 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/IB 96/01049

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9621656	18-07-96	US-A-	5552412	03-09-96
		AU-A-	4091696	18-07-96
		BG-A-	100278	31-05-96
		NO-A-	960081	10-07-96
		PL-A-	312182	22-07-96
		SI-A-	9600004	31-10-96